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One-pot synthesis of 2,3-bis-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinates and arylmethylene-bis-3,3'-quinoline-2-ones

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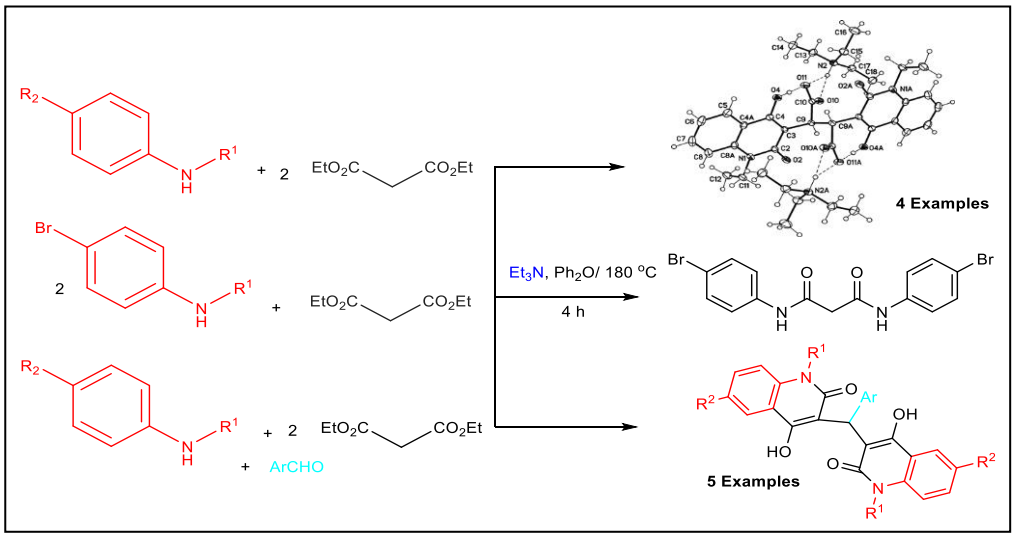
Abstract

In this investigation an efficient synthesis of 2,3-bis-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinic acid derivatives was achieved by one-pot reaction of one equivalent of aromatic amines with two equivalents of diethyl malonate in diphenyl ether and catalyzed with triethyl amine. In case of applying the previous condition with aromatic amines and diethyl malonate in a ratio of 2:1, no quinolone structure was obtained, whereas N^1,N^3-bis(4-bromophenyl)malonamide, as an example, was obtained in 95% yield. Under the same previous condition, arylmethylene-bis-3,3'-quinoline-2-ones were in one pot synthesized *via* the reaction of equal equivalents of aromatic amines and diethyl malonate together with half equivalent of the corresponding aromatic aldehydes. The structure of the obtained compounds was proved by IR, NMR and mass spectra and X-ray structure analyses.



Keywords: Bis-(quinolin-3-yl)succinates, N^1,N^3-bis(4-bromophenyl)malonamide arylmethylene-bis-3,3'-quinoline-2-ones, one-pot synthesis, X-ray

Introduction

2-Quinolones (Chen et al., 2001) have showed considerable interest because of their pharmacological importance (Abass et al., 2015) and various biological activities (Abass et al., 2005). Various quinolones are described to have antimicrobial (Eswaran et al. 2010), antifungal ((Musiol et al., 2006), enzyme inhibitory (Slater et al., 1992) and cytotoxic activities (Ma et al., 2004). The quinolones are also occurred in natural products (Junichiro et al. 2012) mainly in alkaloids (Michael et al. 2005). As for example, quinine is a quinoline based alkaloid structure isolated from the bark of *cinchona* tree (Igarashi J & Kobayashi Y 2005).) and is used for the treatment of malaria. Luotonin (Cagir et al., 2003) is a cytotoxic alkaloid as a Chinese traditional drug, which uses in treatment of rheumatism and inflammation. Quinarcine (Thi et al., 2008) drug is of an acridine-based alkaloid structure which has been used as an antimalarial agent. Kynurenic acid (Turski et al., 1988) is of quinolone structure that can be used for the normal metabolism of amino acids and reveals neuro active activity. Interestingly, antimalarial drugs consist of amino quinoline skeletons (primaquine) and used for the treatment of malaria (Turski et al., 1988).

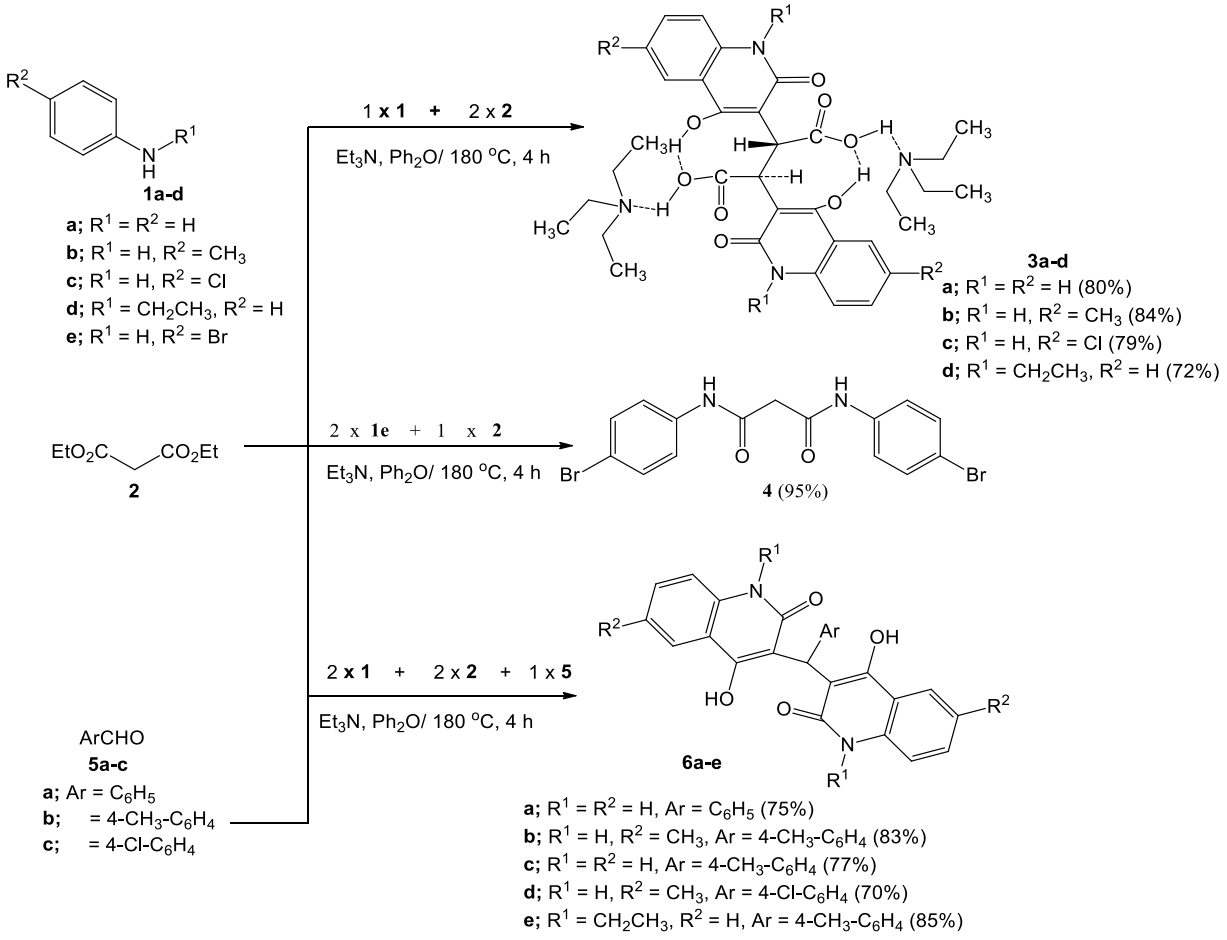
Synthesis of bis-quinolones have recently much attention due to prospective high biological and pharmaceutical activities. For example, functionalized 4,4'-bisquinolones were synthesized by microwave-assisted Pd(0)-catalyzed one-pot borylation/Suzuki cross-coupling reactions or *via* Ni(0)-mediated homocouplings of 4-chloroquinolin-2(1*H*)-one precursors (Hashim et al., 2006). Bis-conjugates of quinine with quinolone antibiotics and amino acid linkers which were retain *in vitro* antimalarial activity with IC_{50} values ranging from 12 to 207 μM, similar to quinine itself (Panda et al., 2012). Recently we have synthesized spiro(indoline-3,4′-pyrano[3,2-*c*]quinoline)-3′-carbonitriles from reaction of quinoline-2,4-diones with 2-(2-oxo-1,2-dihydroindol-3-ylidene)malononitrile (Aly et al., 2018). We also reacted quinolinediones and diethyl acetylene-dicarboxylate to give pyranoquinoline-4-carboxylates and (quinolin-3-yl)fumarates in good yields (El-Sheref et al., 2018). Considering the importance of the interesting chemical behavior of quinolones, and in view of the promising aspects and making a further

stepforward we report herein on the application of the one-pot technique in synthesis of the title compounds.

2. Results and Discussion

To our delight, mixing of one molar proportion of aromatic amines **1a-d** to two molars of diethyl malonate (**2**) in diphenyl ether catalyzed with few drops of triethyl amine (Et_3N) and when the mixture was heated at 180 ^oC for 4 h, the reaction gave 2,3-bis-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinic.bis(triethyl amine) derivatives **3a-d** in 79-84% yields (Scheme 1). The structures of the products were fully consistent with their ^1H NMR, ^{13}C NMR, IR and mass spectra, elemental analyses and X-ray structure analysis as well. We choose compound **3a**, as an example, to confirm the structures. According to elemental analysis spectrometry, the compound **3a** would be in accordance to the molecular weight equals 638.75. In mass spectrum of **3a**, the molecular peak is the base peak and corresponding to the molecular weight of *m/z* 436. One can then conclude the presence of the two molecules of Et_3N in its crystal lattice, which was not noticed in mass spectrum. The latter was confirmed by the NMR spectra of **3a**. The IR spectrum revealed bands at ν 3400, 3210, 1720 and 1680, corresponding to OH, NH, carbonyl-acid and 2-carbonyl-quinolone groups. Figure 1 illustrated the NMR spectroscopic data of compound **3a**, where the ^1H NMR spectrum indicated three singlets, each for two protons at δ 14.10 (COOH), 13.20 (OH), and 11.80 (NH). A quartet resonated at δ 3.17 for twelve protons of $6CH_2$-$2Et_3N$ and a triplet for eighteen protons of $6CH_3$-$2Et_3N$ at δ 1.30 (see the experimental). The two adjacent methine protons were resonated in the ^1H NMR spectrum as a doublet (J = 5.1 Hz) at δ 3.72 indicated that these two protons are in its *trans*-form (Figure 1). The ^{13}C NMR spectrum confirmed the ^1H NMR spectral data by showing the carbonyl-acid and carbonyl-quinolone carbon signals at δ 164.8 and 160.1, respectively. The CH_2- and CH_3-Et_3N appeared at δ = 50.0 and 13.7, whereas the ethano-carbons of succinic acid appeared at δ 38.2. In case of **3d**, the ^1H NMR spectral data revealed the presence of two molecules of Et_3N in its crystal lattice structure as a quartet at δ 3.20 for eighteen protons and a triplet at δ 1.15 for twelve protons. Another two ethyl protons of *N*-1 for quinolone moiety appeared in the ^1H NMR spectrum as a quartet and triplet at δ 3.15

and 1.17, respectively (Experimental Section). The ^{1}H NMR spectrum showed also the two methine protons as a doublet at δ 3.70 (J = 4.6 Hz). The structure of **3d** was then totally proved by X-ray structure analysis (Figure 2).



Scheme 1. One-pot synthesis of 2,3-bis-(4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinates **3a-d**, N^1,N^3-bis(4-bromophenyl)malonamide (**4**) and arylmethylene-bis-3,3'-quinoline-2-ones **6a-e**

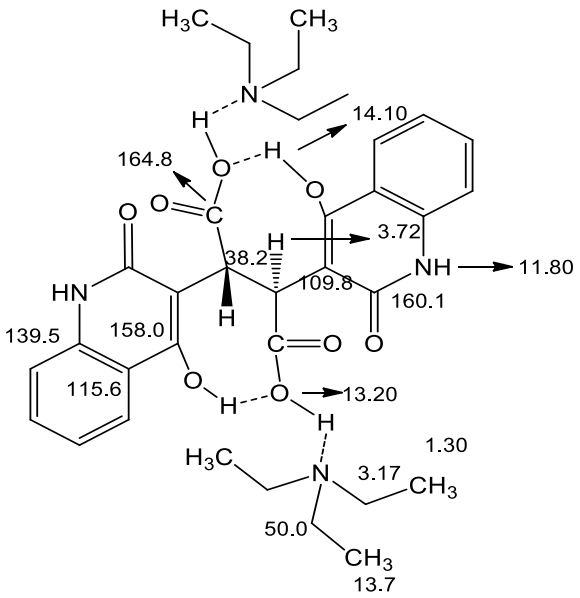


Figure 1. NMR spectroscopic data some distinctive hydrogen protons and carbons of compound **3a**

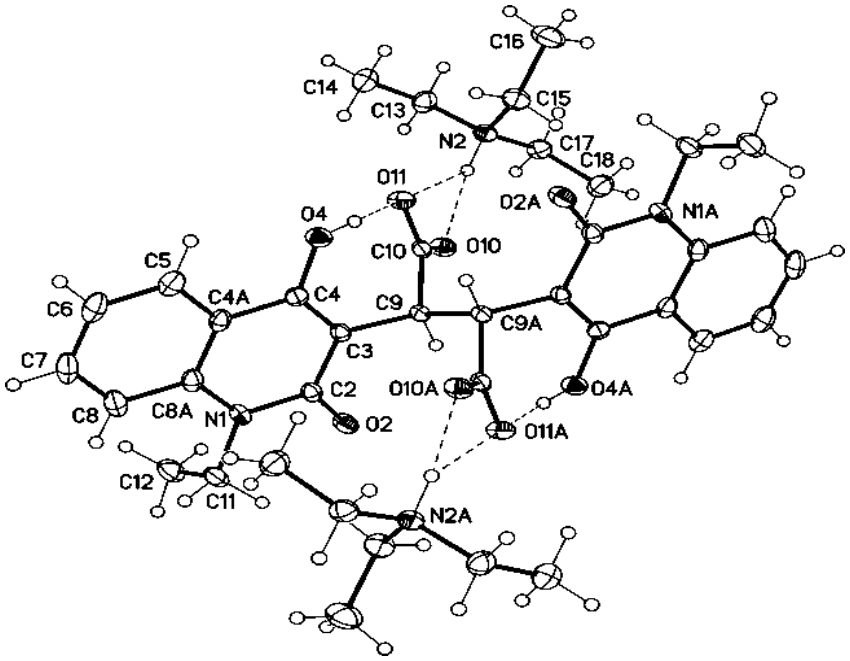
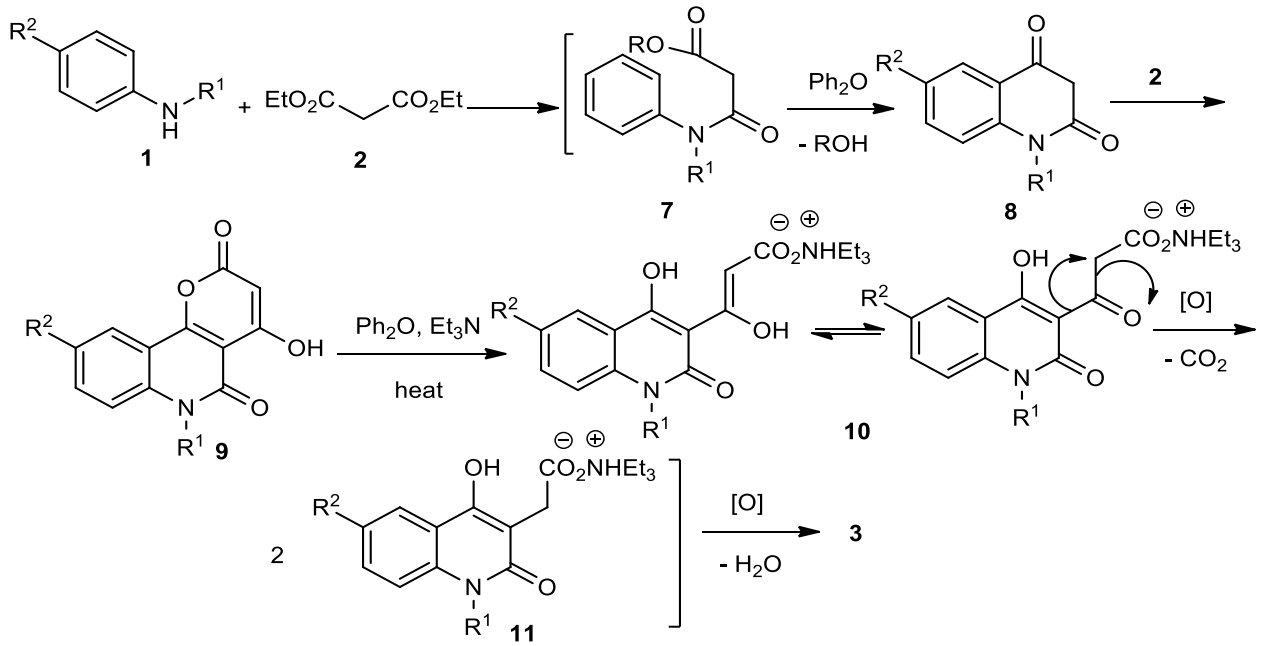


Figure 2. X-ray structure analysis of compound **3d** (displacement parameters are drawn at 50% probability level)

The structure of compounds **3a-d** suffers from the presence of two chiral centers. Therefore, four entantiomeric products should be obtained. One of these enantiomeric products is the *anti*-form. Fortunately, the reaction proceeded to give only one enantiomer. Two types of hydrogen bonds were formed; one was held between the oxygen of the carboxylic-OH and the hydrogen atom of the hydroxyl group of 4-hydroxyquinolone. The other hydrogen bond was held between the nitrogen lone pair in triethyl amine and the hydrogen atom of the free carboxylic-OH. Formation of such two types of hydrogen bonds

would be expected to stabilize the *anti*-form structure of **3a-d** as shown in Scheme 1. The X-ray structure analysis indicated the presence of the two methine protons of succinic acid in its *trans*-form. The *anti*-form of compounds **3a-d** can be identified as the *meso*-form of absolute configuration (*R*,*S*).

It is well-known that both ester enolates and carboxylic acid dianions can be used for oxidative homocoupling. The reaction mechanism can be explained as due to condensation between **1** and **2**, which would form 2-quinolone **8**. Subsequently condensation between **8** and another molecule of **2** would give the fused α-pyranone **9** (Scheme 2). Thermolysis under basic condition of **9** would then give intermediate **10**, which was in equilibrium with entatiomeric form (Scheme 2). Finally, autoxidation of the α-ketonic acid **10** accompanied with elimination of CO_2 and rearrangement would then give salt **11**. Further oxidation of two molecules of **11** would produce target molecule **3** (Scheme 2). To ensure the reaction pathway, we also heat compound **9** in diphenyl ether at 180 ^oC for 3 h and we successfully obtain **3**.



Scheme 2. Proposed mechanism describes the formation of **3**

We should also mention that molar ratios of both compounds **1** and **2**, effect on the formed product. Interestingly, when we carried out the reaction between **1** and **2** in a molar ration of 2:1, we could not separate any quinolonoyl structure and we obtained malonamide **4** (Vennerstrom et al., 1987) (Scheme 1). X-ray structure analysis of **4** is as shown in Figure 3.

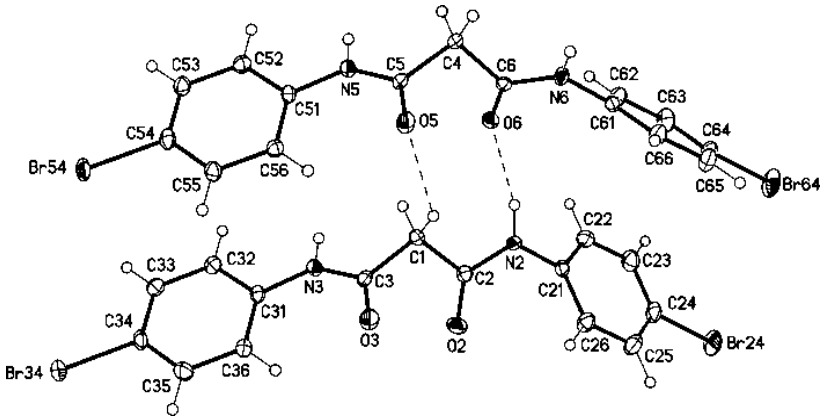


Figure 3. X-ray structure analysis of compound **4**

Inspired by the above results, we extended our studies to react aromatic amines **1a-d** with diethyl malonate (**2b**) and aromatic aldehydes **5a-c** in a molar ratio of 2:2:1 and under the condition mentioned above (Scheme 1). We, surprisingly obtained arylmethylene-bis-3,3'-quinoline-2-ones **6a-e** in good yields as shown in Scheme 1. Previously, it was prepared another derivative of **6** (Bhat & Trivedi et al., 2014**)** by reacting 4-hydroxy-*N*-methylquinolin-2(1*H*)-ones with benzaldehyde derivatives under solvent- and catalyst-free reaction conditions at 80 ^{o}C. The reactants underwent a cascade Knoevenagel–Michael reaction to yield other derivatives **6** in good yields (Bhat & Trivedi et al., 2014**)**. The main difference between our method and the previous method that we prepared compounds **6** in one step in relatively good yields. Moreover, no literatures have discussed the regio accurate structure of **6** (Madhu et al., 2017), weather it is in *anti*- or *syn* form. Besides and to the best of our knowledge, there has not reported NMR spectral data of **6a-e** derivatives.

NMR spectral data of the product **6b** (Figure 4), as an example, which was obtained from the reaction of 4-methylaniline (**1b**), diethyl malonate (**1b**) and *p*-tolualdehyde (**5b**) were illustrated in Table 1. In **6b**; the two quinolinone rings are spectroscopically non-equivalent, although some of their signals co-resonate; the simplest explanation is that their rotation is hindered so that the compound does not possess a σ plane. The 6H methyl singlet at δ 2.38 must be H-6a; its attached carbon appears at δ 20.64. H-6a gives HMBC correlation with carbon signals at δ 131.91 and 122.03; these are assigned as C-7 and C-5 in that order, because the downfield of the two gives HSQC correlation with a 2H doublet at δ 7.42 and the upfield

signal correlates with the nonequivalent 1H singlets at δ 7.79 and 7.69. C-7 also gives HMBC correlation with a 2H doublet at δ 7.33, assigned as H-8; its attached carbon appears at δ 115.34 grounds as C-2,2',4,4'.

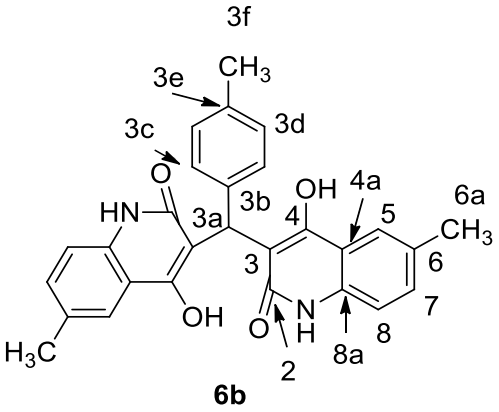


Figure 4. Distinctive carbons of compound **6b**

The *p*-tolyl group is solved similarly: the 3H methyl singlet at δ 2.26 must be H-6f, and gives HSQC correlation to a carbon at δ 20.02. C-3f gives HMBC correlation to a 2H doublet at δ 7.05, assigned as H-3d; its attached carbon appears at δ 128.14. H-3d gives COSY correlation with the remaining 2H doublet at δ 6.96; its attached carbon appears at δ 125.66. H-3c, H-3d, and C-3c also give HMBC correlation with the 1H singlet at δ 6.10, assigned as H-3a; its attached carbon appears at δ 34.43. The four lines between δ 166-160 give HMBC correlation with H-3a, and are assigned on chemical-shift. The remaining seven ^{13}C lines are assigned on chemical-shift grounds as C-3b,4a,6; C-8a; C-3e; and C-3,3' as shown in the Table 1. The upfield shifts of C-3,3' are presumably due to their positions in push-pull systems. Finally X-ray structure analysis of compound **6e** proved its *anti*-form (Figure 5).

Table 1. NMR spectral data of compound **6b**

NMR	**^{1}H-^{1}HCOSY**	**Assignment**
13.18 (s; 1H), 12.73 (s; 1H)		OH
.21 (s; 1H), 12.10 (s; 1H)		NH
79 (s; 1H), 7.69 (s; 1H)	7.42,7.33,*2.38*	H-5,5'
42 (d, *J* = 8.0; 2H)	7.79,7.69,7.33,*2.38*	H-7
33 (d, *J* = 8.4; 2H)	7.79, 7.69, 7.42	H-8
05 (d, *J* = 7.2; 2H)	6.96, 6.10, 2.26	H-3d
96 (d, *J* = 7.6; 2H)	7.05, 6.10	H-3c
10 (s; 1H)	7.05, 6.96, 2.26	H-3a
38 (s; 6H)	7.79, 7.69, 7.42	H-6a

26 (s; 3H)		7.05, 6.10	H-3f

C NMR	HSQC	HMBC	Assignment
165.87, 164.17		6.10	C-2,2’
1.64, 160.69	6.10		C-4,4’
4.56, 134.14, 134.05	7.42,7.05, 6.96, 6.10, 2.26		C-3b,4a,6
1.91	7.42	7.33, 2.38	C-7
1.24			C-8a
8.14	7.05	7.05, 2.26	C-3d
5.66	6.96	6.96, 6.10	C-3c
2.03	7.79, 7.69	7.42, 2.38	C-5
5.99			C-3e
5.34	7.33	7.33	C-8
0.85, 109.22	6.96		C-3,3’
.43	6.10	6.96	C-3a
.64	2.38	7.42	C-6a
.02	2.26	7.05	C-3f

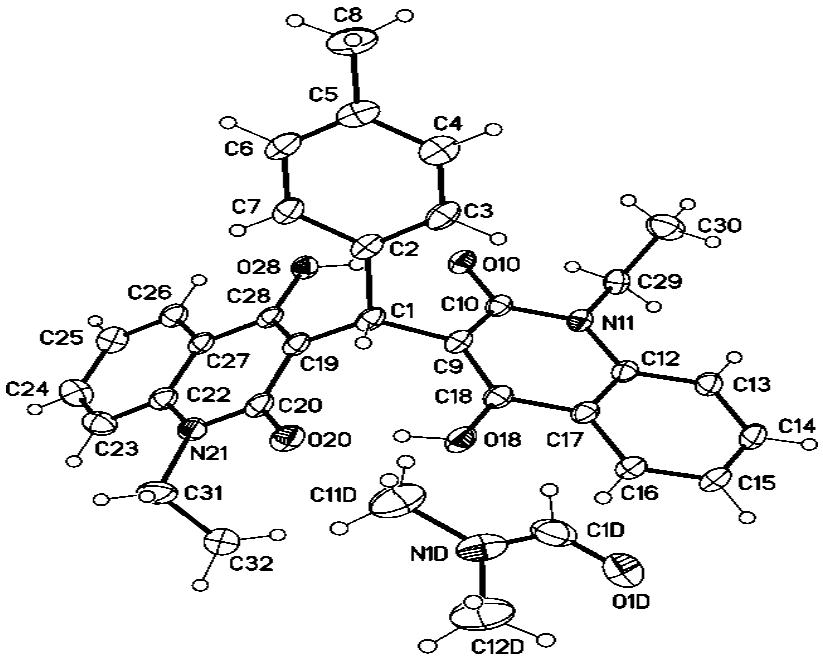
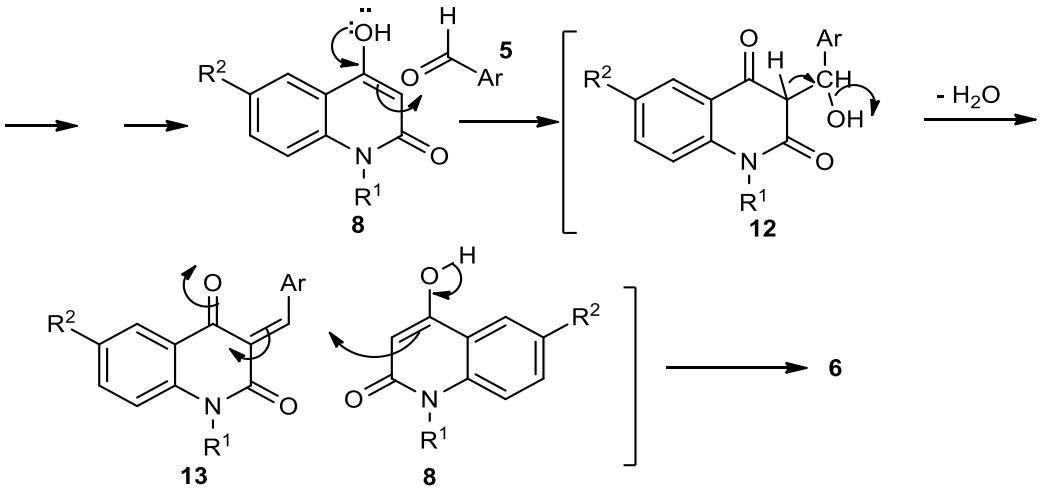


Figure 5. X-ray structure analysis of compound **6e** (minor disordered parts omitted for clarity, displacement parameters are drawn at 50% probability level)

The mechanism can be explained as due to formation of 2-quinolone **8** by the same previous steps mentioned in Scheme 2. Compound **8** would then condense with aldehyde **5** to give intermediate **12** (Scheme 3). Elimination of water molecule from **12** would enable the formation of **13**. Addition of another one molecule of **8** to **13** would, ultimately give **6** (Scheme 3).



Scheme 3. Suggested mechanism describes the formation of **6**

Experimental

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, Loughborough, UK), and are uncorrected. The IR spectra were recorded from potassium bromide disks with a FT device, Minia University NMR spectra were measured in DMSO-d_6 on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.55 MHz for ^{15}N); chemical shifts are expressed in δ (ppm), versus internal tetramethylsilane (TMS) = 0 for ^{1}H and ^{13}C, and external liquid ammonia = 0 for ^{15}N. Coupling constants are stated in Hz. Correlations were established using ^{1}H-^{1}H COSY, and ^{1}H-^{13}C and ^{1}H-^{15}N HSQC and HMBC experiments. Mass spectra were recorded on a Finnigan Fab 70 eV, Institute of Organic Chemistry, Karlsruhe University, Karlsruhe, Germany. TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with Pf_{254} indicator; TLC's were viewed at λ_{max} = 254 nm. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt.

General procedure describes the formation of compounds 3a-d

A mixture of aromatic amines **1a-d** (1 mmol) and **2** (2 mmol) in 50 mL of diphenyl ether and 0.5 mL of Et_3N was fused at 180 ^{o}C for 4 h. The resulting white precipitate was left to cool and then poured in ice cold saturated solution of $NaHCO_3$. The formed precipitate was kept standing up at room temperature for 4 h. The precipitate which was collected by filtration was washed with 200 mL of EtOH and then dried well. The formed product was then recrystallized from stated solvents.

(*R*,*S*)-2,3-Bis(4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)succinate.bis-triethyl amine (3a).

Yellow crystals (DMF), 0.35 g (80%), m.p. 340-2 ^{o}C (decomp).

IR (KBr): $\bar{\upsilon}$ = 3400 (OH), 3210 (NH), 3030-3000 (Ar-CH), 2980-2670 (Aliph-CH), 1720, 1680 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 14.10 (s, 2H, 2COOH), 13.20 (s, 2H, 2OH), 11.80 (s, 2H, 2NH), 8.08 (dd, 2H, *J* = 1.0, 0.8 Hz), 7.60-7.56 (m, 2H), 7.40-7.33 (m, 4H), 3.72 (d, 2H, *J* = 5.1 Hz), 3.17 (q, 12H, 6CH_2-NEt_3), 1.30 ppm (t, 18H, 6CH_3-2NEt_3); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 164.8 (2CO-acid), 160.1 (2CO-quinolone), 158.0 (Ar-2C-OH), 146.7 (Ar-2C), 133.6, 122.9, 122.8, 116.8 (Ar-2H), 111.7, 105.4 (Ar-2C), 50.0 (6CH_2-NEt_3), 38.2 (Aliph-2CH), 13.7 ppm (6CH_3-NEt_3).

MS (70 eV, %): *m/z* = 436 (M-2Et_3N, 100), 306 (30), 282 (52), 153 (92), 136 (65), 106 (25).

Anal for $C_{34}H_{46}N_4O_8$ (638.75): Calcd. 63.93; H, 7.26; N, 8.77. Found: C, 64.00; H, 7.30; N, 8.80.

(*R,S*)-Diethyl 2,3-bis(4-hydroxy-6-methyl-2-oxo-1,2-dihydro-quinolin-3-yl)-succinate (3b).

Yellow crystals (DMF/EtOH), 0.39 g (84%), m.p. 350-2 ^{o}C.

IR (KBr): $\bar{\upsilon}$ = 3460 (OH), 3230 (NH), 3060-3030 (Ar-CH), 2970-2890 (Aliph-CH), 1718, 1682 cm^{-1} (CO).

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 14.20 (s, 2COOH), 13.20 (s, 2H, 2OH), 11.20 (s, 2H, 2NH), 8.15 (d, 2H, *J* = 0.7 Hz), 7.77-7.74 (m, 2H), 6.80 (dd, 2H, *J* = 1.1 Hz), 3.75 (bs, 2H), 3.20 (q, 12H, 6CH_2), 2.20 (s, 6H, 2CH_3), 1.20 ppm (t, 18H, CH_3).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 165.6 (2CO-ester), 162.3 (2CO-quinolone), 158.4 (Ar-2C-OH), 147.2, 137.2, 133.3 (Ar-2C), 126.8, 123.4 (Ar-2H), 112.4, 106.0 (Ar-2C), 50.0 (6CH_2-Et_3N), 37.4 (Aliph-2CH), 21.0 (2CH_3) 14.4 ppm (2CH_3-ester).

MS (70 eV, %): *m/z* = 465 (M-2Et_3N^+, 100), 442 (18).

Anal for $C_{36}H_{50}N_4O_8$ (660.80): Calcd. 64.84; H, 7.56; N, 8.40. Found: C, 64.80; H, 7.60; N, 8.76.

(*R,S*)-Diethyl 2,3-bis(6-chloro-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)succinate (3c).

Yellow crystals (DMF/EtOH), 0.40 g (79%), m.p. 310-2 ^{o}C.

IR (KBr): $\bar{\upsilon}$ = 3400 (OH), 3220 (NH), 3060-3030 (Ar-CH), 2970-2890 (Aliph-CH), 1715, 1672 cm^{-1} (CO).

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 14.20 (s, 2H, 2COOH), 13.20 (s, 2H, 2OH), 11.80 (s, 2H, 2NH), 7.80

(d, 2H, *J* = 0.7 Hz), 7.40 (dd, 2H, *J* = 1.2, 0.8 Hz), 7.15 (dd, 2H, *J* = 1.1, 0.7 Hz, Ar-H), 3.80 (d, 2H, *J* = 5 Hz), 3.20 (q, 12H, CH_2-Et_3N), 1.20 ppm (t, 18H, CH_3-NEt_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.2 (2CO-acid), 162.0 (2CO-quinolone), 157.6 (Ar-2C-OH), 141.6, 135.6, 133.2 (Ar-2C), 128.6, 127.4 (Ar-2H), 113.4, 101.4 (Ar-2C), 50.0 ($6CH_2$-NEt_3), 38.0 (Aliph-2CH), 13.0 ppm ($6CH_3$-ester).

MS (70 eV, %): *m/z* = 505 (M^+, 15), 153 (37), 135 (25), 101 (100).

Anal for $C_{34}H_{44}Cl_2N_4O_8$ (707.64): Calcd. 57.71; H, 6.27; N, 7.92. Found: C, 57.80; H, 6.30; N, 8.00.

(*R*,*S*)-2,3-Bis(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinate.bis-triethyl-ammonium (3d).

Yellow crystals (AcOEt), 0.41 g (82%), m.p. > 350 °C.

IR (KBr): ῡ = 3450-3360 (OH), 3220 (NH), 3060-3020 (Ar-CH), 2960-2810 (Aliph-CH), 1716, 1665 cm^{-1} (CO).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.20 (s, 2H, COOH), 13.30 (s, 2H, 2OH), 7.40-7.35 (m, 4H), 7.25-7.22 (m, 4H), 3.70 (d, 2H, *J* = 4.6 Hz), 3.20 (q, 12H, $6CH_2$-NEt_3), 3.15 (q, 4H, $2CH_2$-NEt_3), 1.17 (t, 6H, $2CH_3$-Et_3N), 1.15 ppm (t, 18H, $6CH_3$-Et_3N).

^{13}C NMR (100 MHz, DMSO-d_6): couldn't be resolved due to bad solubility.

MS (70 eV, %): *m/z* = 492 (M^+, 35), 472 (40), 306 (42), 153 (100), 136 (72).

Anal for $C_{38}H_{54}N_4O_8$ (694.86): Calcd. 65.68; H, 7.83; N, 8.06. Found: C, 65.80; H, 7.70; N, 8.15.

Preparation of compound 4

On repeating the previous procedure, a mixture of aromatic amine **1e** (340 mg, 2 mmol) and **2b** (160 mg, 1 mmol) in 15 mL of diphenyl ether and 0.5 mL of Et_3N was fused at 180 °C for 4 h. The resulting pale-yellow precipitate was left to cool. The formed product was then recrystallized.

***N*^{1},*N*^{3}-Bis(4-bromophenyl)malonamide (4).** Pale yellow crystals (MeOH), 0.40 g (95%), m.p. 330-2 °C (lit (Vennerstrom, J L et al., 1987), 332 °C).

IR (KBr): ῡ = 3230 (NH), 3090-3030 (Ar-CH), 2970-2820 (Aliph-CH), 1685 cm^{-1} (CO).

MS (70 eV, %): *m/z* = 414 (M^{+2}, 18), 412 (M^{+}, 30), 239 (40), 172 (100).

General procedure describes the formation of compounds 6a-e

On repeating the procedure, a mixture of aromatic amines **1a-d** (2 mmol), **2b** (320 mg, 2 mmol) and aromatic aldehydes **5a-c** (1 mmol) in 70 mL of diphenyl ether and 0.5 mL of Et_3N was fused at 180 ºC for 4h. The resulting white precipitate was left to cool and then poured in ice cold saturated solution of $NaHCO_3$. The formed precipitate was kept standing up at room temperature for 24 h. The precipitate which was collected by filtration was washed with about 200 mL of H_2O. The formed product was then washed again with 200 mL of EtOH and dried well. The formed product was then recrystallized from stated solvents.

3,3'-(Phenylmethylene)bis(4-hydroxyquinolin-2(1*H*)-one (6a).

Yellow crystals (DMF/EtOH), 0.360 g (88 %), m.p. 335-7 ºC.

IR (KBr): $\bar{\upsilon}$ = 3390 (OH), 3230 (NH), 3070 (Ar-CH), 2970 (Aliph-CH), 1650 (CO), 1605, 1580 cm^{-1} (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.17 (s; 1H, OH), 12.70 (s, 1H, OH), 12.22 (s, 1H, NH), 12.11 (s, 1H, NH), 7.80 (d 2H, H-5,5'), 7.67 (m 2H, H-6,6'), 7.44 (m 2H, H-7,7'), 7.30 (d 2H, H-8,8'), 7.05-6.96 (m 5H, Ph-H), 6.11 ppm (s; 1H, H-3a).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.71, 164.11 (C-2,2'), 161.33, 160.77 (C-4,4'), 135.60 (C-3b), 134.11 (C-4a), 131.22 (C-7), 130.89 (C-8a), 122.89, 122.86, 116.78 (Ph-CH), 115.11 (C-3,3'), 34.32 ppm (C-3a).

MS (70 eV, %): *m/z* = 410 (M^{+}, 34), 333 (100), 161 (55), 77 (66).

Anal for $C_{25}H_{18}N_2O_4$ (410.42): Calcd. C, 73.16; H, 4.42; N, 6.83. Found: C, 73.22; H, 4.36; N, 6.95.

3,3'-(*p*-Tolylmethylene)bis(4-hydroxy-6-methyl-quinolin-2(1*H*)-one (6b).

Yellow crystals (DMF/EtOH), 0.365 g (80 %), m.p. 358-60 ºC.

IR (KBr): $\bar{\upsilon}$ = 3410 (OH), 3222 (NH), 3045-3020 (Ar-CH), 2989 (Aliph-CH), 1646 (CO), 1610, 1590 cm^{-1} (C=C).

NMR (400 MHz, DMSO-d_6) (Table 1).

MS (70 eV, %): *m/z* = 452 (M^{+}, 38), 361 (100), 187 (24), 91 (66).

Anal for $C_{28}H_{24}N_2O_4$ (452.50): Calcd. C, 74.32; H, 5.35; N, 6.19. Found: C, 74.22; H, 5.43; N, 6.35.

3,3'-(*p*-Tolylmethylene)bis(4-hydroxy-quinolin-2(1*H*)-one (6c).

Yellow crystals (DMF/EtOH), 0.360 g (88%), m.p. > 360 ºC.

IR (KBr): ῡ = 3405 (OH), 3225 (NH), 3091 (Ar-CH), 2956 (Aliph-CH), 1648 (CO), 1600, 1590 cm^{-1} (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.11 (s 1H, OH), 12.78 (s 1H, OH), 12.20 (s 1H, NH), 11.99 (s 1H, NH), 7.81, 7.76 (m, 2H, H-5,5'), 7.42 (m 2H, H-7), 7.03 (d *J* = 7.1 Hz, 2H, H-3d), 6.98 (m 2H, H-3c), 6.12 (s, 1H, H-3a), 2.23 ppm (s, 3H, H-3f).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.80, 164.21 (C-2,2'), 161.63, 159.97 (C-4,4'), 135.55 (C-3b), 134.18 (C-4a), 132.01 (C-8a), 128.66 (C-6), 128.21 (C-3d), 125.08 (C-3c), 123.11 (C-5), 115.78 (C-3e), 115.55 (C-8), 110.99 (C-3,3'), 34.33 (C-3a), 20.10 ppm (C-3f).

MS (70 eV, %): *m/z* = 424 (M^+, 40), 333 (100), 161 (67), 77 (77).

Anal for $C_{26}H_{20}N_2O_4$ (424.45): Calcd. C, 73.57; H, 4.75; N, 6.60. Found: C, 73.65; H, 4.71; N, 6.51.

3,3'-((4-chlorophenyl)methylene)bis(4-hydroxy-6-methylquinolin-2(1*H*)-one) (6d).

Yellow crystals (DMF/EtOH), 0.32 g (68%), m.p. 280-2 ºC.

IR (KBr): ῡ = 3385 (OH), 3210 (NH), 3077 (Ar-CH), 2980 (Aliph-CH), 1646 (CO), 1605, 1588 cm^{-1} (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.21 (s, 1H, OH), 12.70 (s; 1H, OH), 12.21 (s, 1H, NH), 12.08 (s, 1H, NH), 7.77 (s, 2H, H-5,5'), 7.40 (d, *J* = 7.80 Hz, 2H, H-7), 7.03 (d, *J* = 7.0 Hz, 2H, H-3d), 6.97 (d, *J* = 7.2 Hz, 2H, H-3c), 6.10 (s, 1H, H-3a), 2.33 ppm (s, 6H, H-6a).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.67, 164.20 (C-2,2'), 161.66, 160.13 (C-4,4'), 135.54 (C-3b), 134.18 (C-4a), 134.09 (C-6), 131.87 (C-7), 131.11 (C-8a), 130.32 (C-3e), 128.22 (C-3d), 125.18 (C-3c), 122.32 (C-5), 115.48 (C-8), 110.90, 109.66 (C-3,3'), 34.30 (C-3a), 20.55 ppm (C-6a).

MS (70 eV, %): *m/z* = 472 (M^+, 71), 361 (100), 187 (67), 111 (43), 77 (65).

Anal for $C_{27}H_{21}ClN_2O_4$ (472.92): Calcd. C, 68.57; H, 4.48; Cl, 7.50; N, 5.92. Found: C, 68.65; H, 4.55; N, 6.11.

3,3'-(*p*-Tolylmethylene)bis(1-ethyl-4-hydroxy-quinolin-2(1*H*)-one (6e).

Yellow crystals (DMF/EtOH), 0.400 g (83%), m.p. 312-4 ºC.

IR (KBr): $\tilde{\upsilon}$ = 3390 (OH), 3220 (NH), 3052 (Ar-CH), 2988 (Aliph-CH), 1649 (CO), 1600, 1580 cm^{-1} (Ar-C=C).

MS (70 eV, %): *m/z* = 480 (M^+, 71), 389 (100), 189 (32), 91 (43), 77 (50).

Anal for $C_{30}H_{28}N_2O_4$ (480.55): Calcd. C, 74.98; H, 5.87; N, 5.83. Found: C, 75.15; H, 5.75; N, 6.01.

Supporting Information:

Crystal Structure Determinations

The single-crystal X-ray diffraction studies were carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Kα radiation (**3d**, **6e**, λ = 1.54178 Å) or Mo-Kα radiation (**4**, λ = 0.71073 Å). Direct Methods (**3d**, **6e**, SHELXS-97) (Sheldrick et al., 2008) or dual space methods (**4**, SHELXT for **5a**) (Sheldrick et al. 2015) were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) (Sheldrick et al., 2015). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O, N) free). Semi-empirical absorption corrections were applied. For **4** and **6e** an extinction of corrections was applied. In **6e** one NEt-group is disordered. The absolute structure of **4** was determined by refinement of Parsons' x-parameter (Parson et al., 2013).

3d: colourless crystals, $C_{26}H_{22}N_2O_8^{2-} \cdot 2(C_6H_{16}N)^+$, M_r = 694.85, crystal size 0.18 × 0.14 × 0.12 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 9.9912(3) Å, b = 10.7399(3) Å, c = 16.4621(4) Å, β = 94.647(1)°, V = 1760.65(8) $Å^3$, Z = 2, ρ = 1.311 Mg/m^{-3}, μ(Cu-K_α) = 0.747 mm^{-1}, F(000) = 748, $2\theta_{max}$ = 144.2°, 17106 reflections, of which 3467 were independent (R_{int} = 0.025), 232 parameters, 2 restraints, R_1 = 0.039 (for 3201 I > 2σ(I)), wR_2 = 0.106 (all data), S = 1.03, largest diff. peak / hole = 0.303 / -0.237 e $Å^{-3}$.

4: colourless crystals, $C_{15}H_{12}Br_2N_2O_2$, M_r = 412.02, crystal size 0.28 × 0.14 × 0.05 mm, orthorhombic, space group $Pca2_1$ (No. 29), a = 9.5819(4) Å, b = 18.4026(7) Å, c = 16.9824(7) Å, V = 2994.5(2) $Å^3$, Z = 8, ρ = 1.828 Mg/m^{-3}, μ(Mo-K_α) = 5.419 mm^{-1}, F(000) = 1616, $2\theta_{max}$ = 55.4°, 104279 reflections, of which 6908 were independent (R_{int} = 0.048), 392 parameters, 5 restraints, R_1 = 0.028 (for 6424 I > 2σ(I)), wR_2 = 0.063 (all data), S = 1.08, largest diff. peak / hole = 0.754 / -0.420 e $Å^{-3}$, x = 0.000(6).

6e: colourless crystals, $C_{30}H_{28}N_2O_4 \cdot C_3H_7NO$, M_r = 553.64, crystal size 0.38 × 0.30 × 0.24 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 11.4000(5) Å, b = 11.1444(5) Å, c = 22.8990(9) Å, β = 103.551(2)°, V = 2828.2(2) Å^3, Z = 4, ρ = 1.300 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.711 mm^{-1}, F(000) = 1176, $2\theta_{max}$ = 144.0°, 25228 reflections, of which 5552 were independent (R_{int} = 0.023), 379 parameters, 8 restraints, R_1 = 0.037 (for 5095 I > 2σ(I)), wR_2 = 0.101 (all data), S = 1.05, largest diff. peak / hole = 0.270 / -0.245 e Å^{-3}. CCDC 1824942 (**3d**), 1827436 (**4**), and 1824943 (**6e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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